**MICRO CASE 42: C. Difficile**

1. **SIGNS AND SYMPTOMS** 
   1. Fever
   2. abdominal cramping
   3. **frequent diarrhea (six to nine bowel movements per day) for 4 days.**
   4. Three weeks before the current episode, he had undergone a hip replacement and was rehabilitating in an orthopedic unit. During that hospitalization, he developed a nosocomial pneumonia and was treated empirically with cefuroxime and clindamycin.
   5. He gradually improved and was discharged a week before his current presentation, with maintenance oral antibiotics, to recuperate at home. His wife had no similar symptoms.
   6. Physical Exam
      1. appeared confused and very pale.
      2. He could not answer questions about his current condition.
      3. His skin showed decreased turgor
      4. oral mucosa was dry.
   7. Imaging
      1. Sigmoidoscopy revealed erythematous and friable colonic mucosa.
2. **THE SOURCE OF INFECTIOUS ORGANISM.** 
   1. Clostridium difficile-associated diarrhea (CDAD)
3. **THE MANNER OF EXPOSURE, ROUTE OF INFECTION, TISSUES THAT THEY RESIDE AND, WHERE APPROPRIATE, TRANSMISSION TO OTHERS.** 
   1. **The primary (index) cases occur via endogenous mode in precolonized patients exposed to antibiotics**
      1. Antimicrobial agents of all classes and several anticancer chemotherapeutic agents have been incriminated as inciting agents of CDAD. **The most commonly incriminated antimicrobial agents are clindamycin, cephalosporins, and ampicillin.**
   2. **Secondary cases occur via exogenous transmission of spores in the hospital environment and by the hands of health care attendants, causing nosocomial outbreaks**
4. **PATHOGENESIS** 
   1. CDAD is toxin mediated.
   2. C. difficile is ordinarily suppressed by the normal colonic flora, preventing overgrowth but broad-spectrum antibiotics suppress normal flora.
      1. Clindamycin--inhibits growth or kills many different species of anaerobic bacteria in the colon, does not suppress C. difficile.
   3. The overgrowing vegetative organisms of C. difficile produce at least two toxins:
      1. toxin A
      2. toxin B.
   4. Both toxins appear to act by the same mechanism, but **toxin B is more potent**.
   5. Both toxins exert their effects by binding to cellular GTP-binding proteins (in the Rho family within target cells).
   6. The toxins inactivate these proteins by glycosylation, **dysregulating the action of the cytoskeleton** in epithelial cells of the colonic mucosa, and causing **depolymerization of actin**. Break-up of actin filaments causes profound cytopathic effect, damaging the cellular lining of the bowel wall and causing **erythematous and friable colonic mucosa**, ulceration, and hemorrhagic necrosis.
      1. NOTE Pseudomembranous colitis occurs in untreated acute cases and is characterized by multiple elevated, yellowish white plaques (pseudomembranes) within the colon.
         1. Toxic megacolon is a serious sequela of pseudomembranous colitis and may lead to sepsis due to perforation and polymicrobial infection of colonic flora.
5. **METHODS OF IDENTIFICATION AND PLACEMENT INTO A PARTICULAR BIOLOGICAL SUBSET.** 
   1. C. difficile is a strictly **anaerobic** bacterium.
   2. The organisms are **Gram-positive, spore-forming rods**.
   3. Toxigenesis is an important property of diarrheagenic C. difficile.
      1. These strains produce two exotoxins: toxin A and toxin B, which **can be detected by ELISA (sensitive, specific, and simple).**
6. **FACTORS LEADING TO ENHANCED RESISTANCE OR SUSCEPTIBILITY** 
   1. C. difficile is carried asymptomatically as part of the large intestinal flora of 50% of all healthy neonates during the first year of life. The carriage rate decreases to less than 4% in adults. This rate remains constant in the population.
   2. Hospitalized adults who have received antibiotic therapy, carriage rates may be as high as 46% (particularly during outbreaks).
7. **OTHER ORGANISMS IN THE DIFFERENTIAL DIAGNOSIS AND HOW TO DISCRIMINATE AMONG POTENTIAL CAUSATIVE AGENTS.** 
   1. DDX
      1. Antibiotic-associated diarrhea or colitis (Clostridium difficile)
         1. Prior antibiotic use is commonly associated with C. difficile
      2. Bacterial enteritis (dysentery)
         1. Campylobacter
         2. Salmonellosis
      3. Inflammatory bowel disease (IBD)
      4. Irritable bowel syndrome (IBS)
      5. Viral gastroenteritis
      6. Diarrhea has multiple etiologies, and specific clues are usually necessary in addition to microbiologic studies to determine a precise etiology.
         1. Bacterial and viral causes are certainly possible, but they are difficult to distinguish.
         2. Noninfectious causes, such as IBD and IBS, are somewhat less likely to manifest in the elderly but are also important to consider.
         3. Noninfectious causes are often associated with recurrent symptoms and not necessarily a single episode.
   2. Tests
      1. Detection of toxins in the diarrheal stool is the mainstay of delineation of the etiology.
      2. C. diff produces two exotoxins: toxin A and toxin B, which **can be detected by ELISA (sensitive, specific, and simple).**
      3. Culture
         1. C. difficile is a strictly **anaerobic** bacterium.
         2. The organisms are **Gram-positive, spore-forming rods**.
8. **PREVENTION, TREATMENT AND VACCINE DESIGN (LIVE VS. DEAD).** 
   1. **Treatment**
      1. discontinuation of the offending agent
      2. implementation of any necessary supportive measures.
      3. The preferred oral antimicrobial agent is **metronidazole**.
      4. **Oral vancomycin** is an alternative, but its use carries the risk of emergence of vancomycin-resistant enterococci and colonization, which may pose serious health risks. In addition, it is much more expensive.
      5. Relapse is common because C. difficile spores are resistant to many antibiotics, and continued antibiotic use can delay the return of
         normal flora that would inhibit growth of C. difficile.
   2. **Prevention**
      1. Limiting use of broad-spectrum antibiotics
      2. Measures to control the spread of infection within the hospital include hand washing, removing gloves before attending another patient, enteric precautions, and isolating the index case or cohort patients with CDAD.